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09/450,217	11/29/1999	PETER ERDMANN	8265-296-999	7310

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EXAMINER	
LUKTON, DAVID	

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1653	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/450,217	Applicant(s) ERDMANN ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-19 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *14-19 and 21-23* is/are withdrawn from consideration.

5)☒ Claim(s) *6 and 7* is/are allowed.

6)☒ Claim(s) *1-4,8-13 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 21 (filed 7/17/03), claims 1, 9, 12, 24, 25 have been amended. Claims 1-4, 6-19, 21-26 remain pending. Claims 14-19 and 21-23 remain withdrawn from consideration. Claims 1-4, 6-13, 24-26 are examined in this Office action.

Applicants' arguments filed 7/17/03 have been considered and found persuasive in part. The rejection of claims 1-4, 8-13, 24-25 over Kawasaki (USP 5,278,288) is withdrawn.

Claims 6-7 are characterized as allowable.

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Claim 8 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the phrase "between about 4.5 to 5.5", thus rendering the claim indefinite as to the upper and lower limits of pH.

In the response filed 7/27/03, it is argued that the term "about" is supported by the specifcation. However, no rejection for new matter has been imposed. Next, it is argued that other examiners have abstained from rejecting claims which contain the term at issue; such an argument, however, does not make the claim clear. Next it is argued that the exact pH is not critical. However, when the pH is less than 4.5 (for example, 4.3), a contradiction arises between the requirement that the pH be "between" 4.5 and 5, and the requirement that the pH be less than 4.5. Thus, one of the key questions here is, must the

pH be 4.5 or greater, or can the pH be less than 4.5...? It is unclear whether the term "about" is controlling, or whether the term "between [two endpoints]" is controlling.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-4, 9-13, 24-25 are rejected under 35 U.S.C. §103 as being unpatentable over Shimatani (USP 5,434,250); or Shimatani in view of Scopes (*Protein Purification*, pages 68-75, 1982).

As indicated previously, Shimatani teaches (beginning at col 2, line 67) a process of obtaining GMP by passing desalted whey, at acidic pH, through a cation exchanger. Additionally, claim 5 of the patent (col 6, line 23+) teaches a process of obtaining GMP by passing whey, at acidic pH, through a cation exchanger, and then employing the further step of ultrafiltration. Shimatani does not provide a detailed analyis of the factors affecting adsorption of proteins to ion exchange resins. Scopes provides a discussion of the theory

behind binding of proteins to ion exchange resins. Scopes makes no mention of GMP.

In the response filed 7/17/03, it is argued that the claims now require that GMP be removed from the lactic raw material by adsorbing the GMP onto a cation exchange resin. However, this is not what the claims require. The claims permit any chromatographic procedure involving a cation exchange column, provided that at a finite (though not necessarily perceptible) degree of adsorption of GMP occur. The claims do not require that any component of the lactic raw material be separated from any other component of the lactic raw material as a consequence of GMP being adsorbed to the resin. Furthermore, the claims do not actually require that the GMP be obtained in pure form, or anything approaching pure form. The claims, in fact, encompass the possibility of "obtaining" a mixture in which GMP is only 5% of the total. This is because the claims are drawn to a method of obtaining a fraction that contains GMP; the requirement that the fraction be "enriched" in GMP is met if the concentration of GMP is higher at the end than it was in the beginning. As indicated in the previous Office action, a "lactic raw material" could be e.g., a mixture of GMP in combination with *alpha*-casein, albumin, and lactollin. Or a "lactic raw material" could be e.g., a mixture of GMP in combination with albumin, IgG, and *alpha*-lactoglobulin. The requirement that a "fraction" be obtained (claim 1) is met if one begins with a mixture that contains 20 components (of which GMP is one), and succeeds only in removing one of those 20 components. Having eliminated just one of the 20 components, the resulting mixture is "enriched" in GMP. Thus, the claims

encompass the possibility of obtaining a complex mixture of which GMP is but one minor component.

The principle basis of traversal is that Shimatani fails to disclose that GMP becomes adsorbed to the anionic resin. However, Shimatani does imply that a small degree of adsorption does occur. The important point to be made here is that the claims do not require that the degree of adsorption be sufficient to be of any consequence. If a given protein is subjected to ion exchange chromatography, and completely elutes within 1.5 times the "void" volume, one can say that a small degree of adsorption has occurred. As a practical matter, if a "second" molecule (e.g., a polysaccharide, amino acid, or inorganic compound) completely elutes within the void volume, the difference in adsorption (between the protein and the "second" molecule) would not be sufficient to achieve a separation between the two compounds. Under such a scenario, a chromatographer might say that the adsorption of the protein and the "second" molecule is inconsequential. But the fact remains that if a compound requires more than the void volume in which to elute, some adsorption has occurred. This issue is also discussed in Scopes, especially at pages 72-73. For example, figure 4.3 shows the behavior of a mixture of two proteins, one exhibiting an "alpha" value of zero (indicating no adsorption) and the other an alpha of 0.4 (indicating a small degree of adsorption). Despite the fact that the latter protein eluted within just two column volumes, its "alpha" value was still well above zero. Using the terminology of Scopes, instant claim 1 would encompass the possibility that the "alpha"

value of the GMP is just 0.09, which would mean that most (but not all) of the GMP would elute in the void volume. Consider col 3, lines 5-12 of Shimatani. This passage states that if a mixture of *beta*-Lg, *alpha*-Lg and GMP is contacted with an anionic resin at a pH of 2-4, the *beta*-Lg is adsorbed to a greater degree than is the *alpha*-Lg, and that the *alpha*-Lg is eventually eluted. This does not mean, however, that no adsorption of the *alpha*-Lg occurred at all. The passage simply means that the difference in degree of adsorption was sufficiently great that a separation (between *alpha*- and *beta*-Lg) could be obtained. The passage at issue (col 3, lines 5-12) also implies that the degree of adsorption of the GMP was even greater than that of the *alpha*-Lg (though substantially less than that of the *beta*-Lg). This is because, as conveyed in the passage at col 3, lines 11-12, some of the GMP is retained under conditions in which *alpha*-Lg is eluted. One might ask whether GMP could be readily separated from a compound eluting in the void volume under the conditions disclosed in Shimatani. The answer might be yes, and it might be no, but the question is moot. The claims require only that a finite degree of adsorption occur, however small that might be, and not whether the degree of adsorption is sufficient to be of any practical consequence to a chromatographic specialist. The chromatographic specialist of ordinary skill would have concluded that under the conditions set forth in Shimatani, a small but finite degree of adsorption occurred between the anionic resin and the GMP.

It is also argued (response filed 7/17/03) that Shimatani does not disclose the step of eluting the adsorbed GMP from the resin. However, the step of eluting the GMP is taught

in several locations such as col 3, lines 5-12 and col 6, lines 23+. An "exchanger passed solution" is one in which the GMP has been eluted from the resin.

It is also argued (response filed 7/17/03) that Shimatani discloses ultrafiltration in conjunction with ion exchange chromatography. However, the claimed invention does not exclude ultrafiltration. In addition, the limitations of the claims are met by Shimatani even without the ultrafiltration step. As indicated above, the claims are not drawn to a method of obtaining pure GMP. Instead, the claims encompass the possibility of obtaining, at the end of the claimed process, a complex mixture of which GMP is but one minor component.

The rejection is maintained.

*

Claims 1-4, 9-13, 24-25 are rejected under 35 U.S.C. §103 as being unpatentable over Shimatani (USP 5,434,250) view of Marshall (*Food Research Quarterly* **51**, 1991), further in view of Scopes (*Protein Purification*, pages 75-101, 1982).

As indicated previously, Shimatani teaches (beginning at col 2, line 67) a process of obtaining GMP by passing desalted whey, at acidic pH, through a cation exchanger. Additionally, claim 5 of the patent (col 6, line 23+) teaches a process of obtaining GMP by passing whey, at acidic pH, through a cation exchanger, and then employing the further step of ultrafiltration. Also disclosed (col 3, line 63+) that GMP is a monomer at a pH below 4, but a polymer at a pH above 4. Shimatani does not disclose that GMP

is useful in food products. Shimatani also does not disclose a method of chromatography in which GMP is retained on a cation exchange column. Marshall discloses that GMP is useful in food products. Marshall does not teach the claimed process. Scopes provides a discussion of techniques in ion exchange chromatography, and conveys that at a pH below the pKa of a protein, a cation exchange column should be used, and at a pH above the pKa of a protein, an anion exchange column should be used. Scopes makes no mention of GMP.

The claims require that the deionization step be undertaken at a pH in the range of 1 to 4.5. However, the claims impose no limits on what the pH should be once the GMP-containing material is contacted with the cation exchange resin. Thus, any and all pH's are encompassed, as long as a finite degree of adsorption can be obtained. The protein chemist of ordinary skill would have been motivated by Marshall to achieve at least a partial purification of the GMP, for the benefits disclosed therein. The protein chemist of ordinary skill would have taken from Scopes the information that in order to achieve a high degree of binding between a protein and a cation exchange column, the pH should be sufficiently low as to achieve a net positive charge on the protein. It is well within the ability of the ordinarily skilled protein chemist to determine what pH might be required in order to achieve such binding; whatever pH might be optimal is not relevant to the question of obviousness, since the instant claims impose no limitations on the pH of the eluting buffer.

Thus, the protein chemist of ordinary skill endeavoring to obtain a partial purification of GMP would have been motivated to use cation exchange chromatography using whatever pH is appropriate to achieve binding of the GMP to the resin.

The claims are rendered obvious.

*

Claims 1-4, 9-13, 24-25 are rejected under 35 U.S.C. §103 as being unpatentable over Kawasaki (USP 5278288) in view of Scopes (*Protein Purification*, pages 75-101, 1982).

Kawasaki discloses (col 2, line 62+) a process of preparing GMP by contacting milk raw materials with a cation exchanger. The recommended pH is in the range of 3-4.5 (col 3, line 62+) . Also disclosed (col 4, line 17+) is that GMP polymerizes above pH 4. Also disclosed (col 1, line 8+) is that GMP has useful physiological properties. Kawasaki does not disclose that, after completing the process, a further purification of the GMP should be undertaken.

The claims require that the deionization step be undertaken at a pH in the range of 1 to 4.5. However, the claims impose no limits on what the pH should be once the GMP-containing material is contacted with the cation exchange resin. Thus, any and all pH's are encompassed, as long as a finite degree of adsorption can be obtained. The protein chemist of ordinary skill, having completed the Kawasaki process, and intending to use the GMP to achieve a "physiological activity" would have been motivated to achieve a further purification of the GMP. The protein chemist of ordinary skill would

have taken from Scopes the information that in order to achieve a high degree of binding between a protein and a cation exchange column, the pH should be sufficiently low as to achieve a net positive charge on the protein. It is well within the ability of the ordinarily skilled protein chemist to determine what pH might be required in order to achieve such binding; whatever pH might be optimal is not relevant to the question of obviousness, since the instant claims impose no limitations on the pH of the eluting buffer.

Thus, the claims are rendered obvious.

*

Claims 25-26 are rejected under 35 U.S.C. §103 as being unpatentable over Shimatani (USP 5,434,250) in view of Drouet (USP 5,063,203).

The teachings of Shimatani were indicated previously. Shimatani does not disclose that GMP inhibits thrombosis. Drouet discloses that GMP inhibits thrombosis, but does not disclose the claimed process.

In the response filed 7/17/03, it is argued that Shimatani fails to suggest that a small but finite degree of adsorption occurs between the resin and the GMP. However, as indicated above, a small degree of adsorption is suggested.

The rejection is maintained.

*

Claims 25-26 are rejected under 35 U.S.C. §103 as being unpatentable over Kawasaki

(USP 5,278,288) in view of Scopes (*Protein Purification*, pages 75-101, 1982), further in view of Drouet (USP 5,063,203).

The teachings of Kawasaki are indicated above. Kawasaki does not disclose that GMP inhibits thrombosis. As indicated above, Scopes discusses methods of ion exchange chromatography, but does not mention GMP. Drouet discloses that GMP inhibits thrombosis, but does not disclose the claimed process.

As indicated above, the protein chemist of ordinary skill would have been motivated to undertake a second purification process using ion exchange chromatography in order to obtain a product useful for inhibiting thrombosis. The comments made above are (Kawasaki in view of Scopes) are incorporated herein.

The claims are rendered obvious.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CHRISTOPHER S. F. LOW
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9/30/03

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